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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/051,455	04/21/93	MASINOVSKY B	FHIC16963

KOH, C EXAMINER

18N1/0825

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ART UNIT	PAPER NUMBER
1815	4

DATE MAILED: 08/25/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ___ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-18 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 5-16 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-4 and 17-18 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).

12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide written description of the invention and failing to provide enabling disclosure for the in vivo utility.

It appears that "the agent that specifically binds to IL-4 activated microvascular endothelial cells" and the "binding partners that bind to the IL-4 activated microvascular endothelial cells" are the same "mAb6G10 produced by hybridoma with ATCC No.. But it is noted on page 4, line 16 , page 21, line 11, and page 29, line 18 of the specification that ATTC No. is missing.

Therefore, applicant is advised to provide the missing information in response to this office action in order to overcome the objection to the specification.

In addition to the above, the specification lacks enablement for in vivo use of IL-4 or IL-1ß as set forth in claims 1-4 and also in vivo use of "an agent that specifically binds to IL4-activated microvascular endothelial cells" as set forth in claims 17-18.

The specification neither teaches how to administer the active agents nor what "an effective amount" for in vivo administration is.

The disclosure of "inconclusive" result of IL-4 effect on lymphocyte adhesion suggesting that "VCAM-1 might contribute to the process of lymphocyte attachment" (see page 15, lines 11-14) to microvascular endothelial cells or the conclusion based on the in vitro experimental data, such as antibody binding assay (see page 15, lines 31-34) cannot be accepted as the evidence of in vivo activity of IL-4, because it is unpredictable as to how IL-4 would interact with other cytokines in in vivo settings and how the binding agent would react with other existing VCAMs in endothelial cells in vivo.

Claims 1-4 and 17-18 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 2, 4, and 17-18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 4 depends on claims 1 and 3 which lack antecedent basis for IL-1ß. It is not clear whether the claims are drawn to the administration of IL-1ß in combination with IL-4 or IL-1ß is administered instead of IL-4.

Even though the functional limitation such as "an agent specifically binds to IL4-activated microvascular endothelial cells" is set forth, because the term "an agent" in claims 17-18 are not clearly defined, it would take undue experimentation to determine which agent would have the activity required to carry out the invention. Therefore, "agent" in the claims fails to set the metes and bounds of the claims.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-4 are rejected under 35 U.S.C. § 103 as being unpatentable over any one of Thornhill et al (Ref. 52) or Masinovsky et al (Ref. R) in view of Munro et al or Cotran (Ref. 10).

Thornhill et al (Ref. 52) disclose that IL-4 increases adhesion of lymphocytes to endothelial cells (EC) and suggests that the increased binding results from the increased expression or accessibility of EC surface receptors for lymphocytes.

Masinovsky et al (Ref. R) disclose that the first step of the process of lymphocyte migration from the blood stream into surrounding tissues involves specific binding of lymphocytes to adhesive ligands expressed by microvascular endothelial cells in lymphoid organs, and teaches that not only each of IL-4 or IL-1ß alone increases adhesion of peripheral blood lymphocytes to the endothelial cells but also they act synergistically.

Neither Thornhill et al nor Masinovsky et al reference disclose the claimed method of "modulating the immune response" or "treating inflammation" and actually administering IL-4 or IL-1ß to a patient as claimed.

However, since it is well established in the art that adhesion of lymphocytes to endothelial cells (EC) is the requisite first element in the multistep process of transmigration from blood across the postcapillary venules, it would have been obvious to a person having ordinary skill in the art at the time of the invention to use IL-4 or IL-1ß alone or in combination to increase adhesion of peripheral blood lymphocytes to the endothelial cells with a reasonable expectation of success in promoting transmigration of lymphocytes as claimed.

In addition to the above, it is well recognized in the art that in vivo inflammatory endothelial cell changes are paralleled by in vitro phenotypic and morphologic alterations that can be induced by exposure to cytokines as disclosed by Munro et al (see page 121) or Cotran (Ref. 10, page 412), and it is also known that in inflammatory reactions cytokines activate the endothelium to promote lymphocyte adherence and migration into the inflammatory site and the modulation of such cell-mediated immune response are known to be effective in treating inflammation.

In view of the art recognized correlations discussed above, it would also have been obvious to one of ordinary skill in the art to use agents that promote lymphocyte adhesion to endothelial cells and promote transmigration of lymphocytes from blood across postcapillary venules at sites of inflammation with a reasonable expectation of success in modulating immune response or treating inflammation, respectively.

Claims 17-18 are rejected under 35 U.S.C. § 103 as being unpatentable over Thornhill et al as applied to claims 1-4 above, and further in view of Osborn et al (Ref. 29).

Thornhill et al reference is discussed above.

Thornhill et al, however, do not disclose a specific vascular adhesion molecule involved in lymphocyte adhesion.

Osborn et al (Ref. 29) disclose a vascular cell adhesion molecule, VCAM-1, which is induced by cytokines on human endothelial cells and binds lymphocytes and suggests the involvement of VCAM-1 in the involvement of lymphocyte recruitment into inflammatory sites. (see page 1203)

As discussed above, since it is well established in the art that the transmigration of lymphocytes across postcapillary venules requires the adhesion of lymphocytes to microvascular endothelial cells and the binding of specific lymphocytes occurs via a specific vascular cell adhesion molecule, one of ordinary skill in the art would also be motivated to use an agent that binds to cytokine-activated microvascular endothelial cells to block lymphocyte-EC adhesion, with a reasonable expectation of success in impeding transmigration of lymphocytes.

"Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4227."

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1811. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Choon P. Koh whose telephone number is (703) 308-2973.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Choon P. Koh
August 19, 1993

MICHAEL G. WITYSHYN
SUPERVISORY PATENT EXAMINER
GROUP 1800
8-21